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PATENT
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IN THE U.S. PATENT AND TRADEMARK OFFICE

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12/28/01

Applicant:	TEUBER, Lene et al.	Conf.:	
Appl. No.:	New	Group:	
Filed:	December 28, 2001	Examiner:	
For:	POTASSIUM CHANNEL BLOCKING AGENTS		

L E T T E R

Assistant Commissioner for Patents
Washington, DC 20231

December 28, 2001

Sir:

Under the provisions of 35 U.S.C. § 119 and 37 C.F.R. § 1.55(a), the applicant(s) hereby claim(s) the right of priority based on the following application(s):

Country	Application No.	Filed
DENMARK	PA 1999 00927	June 29, 1999

A certified copy of the above-noted application(s) is(are) attached hereto.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fee required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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GMM/rem
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Attachment

(Rev. 10/31/01)

TEUBER, Lene et al.
BSKB
703-205-8000
Dec. 28, 2001
2815-0187P
1 of 1
#5

Kongeriget Danmark

Patent application No.: PA 1999 00927

Date of filing: 29 June 1999

Applicant: NeuroSearch A/S
Smedeland 26B
DK-2600 Glostrup

This is to certify the correctness of the following information:

The attached photocopy is a true copy of the following document:

- The specification, claims and abstract as filed with the application on the filing date indicated above.

Patent- og Varemærkestyrelsen · Kongeriget Danmark ·

Patent- og
Varemærkestyrelsen
Erhvervsministeriet

Taastrup 13 November 2001

Karin Schlichting
Head Clerk

POTASSIUM CHANNEL BLOCKING AGENTS

TECHNICAL FIELD

This invention relates to novel potassium channel blocking agents, and their use in the preparation of pharmaceutical compositions.

Moreover the invention is directed to pharmaceutical compositions useful for the treatment or alleviation of diseases or disorders associated with the activity of potassium channels, in particular asthma, cystic fibrosis, chronic obstructive pulmonary disease and rhinorrhea, convulsions, vascular spasms, coronary artery spasms, renal disorders, polycystic kidney disease, bladder spasms, urinary incontinence, bladder outflow obstruction, irritable bowel syndrome, gastrointestinal dysfunction, secretory diarrhoea, ischaemia, cerebral ischaemia, ischaemic hearth disease, angina pectoris, coronary hearth disease, traumatic brain injury, psychosis, anxiety, depression, dementia, memory and attention deficits, Alzheimer's disease, dysmenorrhea, narcolepsy, Reynaud's disease, intermittent claudication, Sjorgren's syndrome, migraine, arrhythmia, hypertension, absence seizures, myotonic muscle dystrophia, xerostomi, diabetes type II, hyperinsulinemia, premature labour, baldness, cancer, and immune suppression.

BACKGROUND ART

Ion channels are transmembrane proteins, which catalyse the transport of inorganic ions across cell membranes. The ion channels participate in processes as diverse as the generation and timing of action potentials, synaptic transmissions, secretion of hormones, contraction of muscles, etc.

All mammalian cells express potassium (K^+) channels in their cell membranes, and the channels play a dominant role in the regulation of the membrane potential. In nerve and muscle cells they regulate the frequency and form of the action potential, the release of neurotransmitters, and the degree of broncho- and vasodilation.

From a molecular point of view, the K^+ channels represent the largest and most diverse group of ion channels. For an overview they can be divided into five large

subfamilies: Voltage-activated K^+ channels (K_v), long QT related K^+ channels (KvLQT), inward rectifiers (K_{IR}), two-pore K^+ channels (K_{TP}), and calcium-activated K^+ channels (K_{ca}).

The latter group, the Ca^{2+}-activated K^+ channels, consists of three well-defined subtypes: SK channels, IK channels and BK channels. SK, IK and BK refer to the single-channel conductance (**S**mall, **I**ntermediate and **B**ig conductance **K** channel). The SK, IK, and BK channels exhibit differences in e.g. voltage- and calcium-sensitivity, pharmacology, distribution and function.

SK channels are present in many central neurons and ganglia, where their primary function is to hyperpolarize nerve cells following one or several action potentials, in order to prevent long trains of epileptogenic activity to occur. The SK channels are also present in several peripheral cells including skeletal muscle, gland cells, liver cells, and T-lymphocytes. The significance of SK channels in normal skeletal muscle is not clear, but their number is significantly increased in denervated muscle, and the large number of SK channels in the muscle of patients with myotonic muscle dystrophia, suggest a role in the pathogenesis of the disease.

Studies indicate that K^+ channels may be a therapeutic target in the treatment of a number of diseases including asthma, cystic fibrosis, chronic obstructive pulmonary disease and rhinorrhea, convulsions, vascular spasms, coronary artery spasms, renal disorders, polycystic kidney disease, bladder spasms, urinary incontinence, bladder outflow obstruction, irritable bowel syndrome, gastrointestinal dysfunction, secretory diarrhoea, ischaemia, cerebral ischaemia, ischaemic hearth disease, angina pectoris, coronary hearth disease, traumatic brain injury, psychosis, anxiety, depression, dementia, memory and attention deficits, Alzheimer's disease, dysmenorrhea, narcolepsy, Reynaud's disease, intermittent claudication, Sjorgren's syndrome, migraine, arrhythmia, hypertension, absence seizures, myotonic muscle dystrophia, xerostomi, diabetes type II, hyperinsulinemia, premature labour, baldness, cancer, and immune suppression.

A number of neuromuscular blocking agents with effect on SK channels exist, e.g. apamin, atracurium, pancuronium and tubocurarine.

WO 97/48705 discloses a particular group of chemical compounds useful as calcium activated potassium channel blocking agents. However, their selectivity in respect of the SK channel is not disclosed.

US 5739127 and US 5760230 disclose other groups of chemical compounds acting on potassium channels.

SUMMARY OF THE INVENTION

The present invention resides in the provision of novel chemical compounds capable of selectively blocking SK channels, or subtypes of SK channels.

Moreover the invention is directed to pharmaceutical compositions useful for the treatment or alleviation of diseases or disorders associated with the activity of potassium channels, including diseases or conditions like respiratory diseases such as asthma, cystic fibrosis, chronic obstructive pulmonary disease and rhinorrhea, convulsions, vascular spasms, coronary artery spasms, renal disorders, polycystic kidney disease, bladder spasms, urinary incontinence, bladder outflow obstruction, irritable bowel syndrome, gastrointestinal dysfunction, secretory diarrhoea, ischaemia, cerebral ischaemia, ischaemic hearth disease, angina pectoris, coronary hearth disease, traumatic brain injury, psychosis, anxiety, depression, dementia, memory and attention deficits, Alzheimer's disease, dysmenorrhea, narcolepsy, Reynaud's disease, intermittent claudication, Sjorgren's syndrome, migraine, arrhythmia, hypertension, absence seizures, myotonic muscle dystrophia, xerostomi, diabetes type II, hyperinsulinemia, premature labour, baldness, cancer, and immune suppression.

Accordingly, in its first aspect, the invention provides novel chemical compounds selected from the group represented by the general formulas I to IV, below.

In another aspect, the invention provides pharmaceutical compositions comprising an effective amount of a chemical compound of the invention.

In further aspects the invention relates to the use of a chemical compound of the invention for the manufacture of a medicament for the treatment or alleviation of diseases or disorders associated with the activity of potassium channels, and to method of treatment or alleviation of disorders or conditions responsive to blockade of potassium channels.

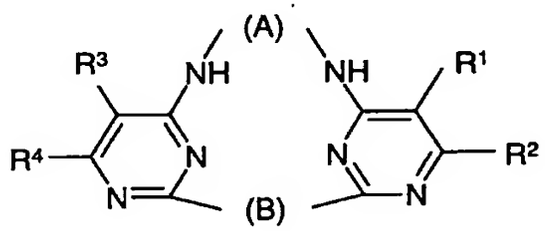
DETAILED DISCLOSURE OF THE INVENTION

Potassium Channel Bl cking Agent

In its first aspect, the invention provides novel cyclic bis-diamino quinazolines. The novel chemical compounds of the invention is particularly useful as potassium channel blocking agents.

Therefore, the invention provides a potassium channel blocking agent, in particular a SK channel blocking agent, selected from the group represented by the general formulas I to IV, below.

Formula I



(I)

wherein

A and B, independently of each another, represent a linking group having a chain length comprising of from 1 to 20 separate bonds; and

R^1, R^2, R^3 and R^4, independently of each another, represent

hydrogen, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, amino, trihalogenmethyl, nitro, cyano, or a group of the formula -OR', -SR', -R'OR", -R'SR", -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', -C(S)SR', -C(O)NR'(OR"), -C(S)NR'(OR"), -C(O)NR'(SR"), -C(S)NR'(SR"), $-CH(CN)_2$, $-C(O)NR'_2$, $-C(S)NR'_2$, $-CH[C(O)R']_2$, $-CH[C(S)R']_2$, $-CH[C(O)OR']_2$, $-CH[C(S)OR']_2$, $-CH[C(O)SR']_2$, $-CH[C(S)SR']_2$, CH_2OR', CH_2SR', or $-SO_2NR'R"$;

a partially or completely saturated mono- or polycyclic group, a mono- or poly-heterocyclic group, an aralkyl group, or a hetero-alkyl group, which mono- or polycyclic groups or aralkyl or hetero-alkyl groups may optionally be substituted one or more times with substituents selected from the group consisting of halogen, trihalogenmethyl, alkyl, alkenyl, alkynyl, amino, nitro,

cyano, or amido, or a group of the formula -R', -OR', -SR', -R'OR", -R'SR", -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', or -C(S)SR'; or

a phenyl or a phenoxy group, which phenyl or phenoxy groups may optionally be substituted on or more times with substituents selected from the group consisting of halogen, trihalogenmethyl, alkyl, alkenyl, alkynyl, amino, nitro, cyano, or amido, or a group of the formula -R', -OR', -SR', -R'OR", -R'SR", -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', or -C(S)SR'; or

R^1 and R^2 together, or R^3 and R^4 together, form a partially or completely saturated mono- or polycyclic group, or a mono- or poly-heterocyclic group, which mono- or polycyclic groups may optionally be substituted one or more times with substituents selected from the group consisting of

halogen, trihalogenmethyl, alkyl, alkenyl, alkynyl, amino, nitro, cyano, or amido, or a group of the formula -R', -OR', -SR', -R'OR", -R'SR", -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', or -C(S)SR'; or

a phenyl or a phenoxy group, which phenyl or phenoxy groups may optionally be substituted on or more times with substituents selected from the group consisting of halogen, trihalogenmethyl, alkyl, alkenyl, alkynyl, amino, nitro, cyano, or amido, or a group of the formula -R', -OR', -SR', -R'OR", -R'SR", -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', or -C(S)SR';

wherein R' and R", independently of each another, represent hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy or alkoxyalkyl, or a group of the formula NR'"R"", wherein R'" and R"", independently of each another, represent hydrogen or an alkyl group.

In a preferred embodiment, A and B, independently of each another, represent

a linear or branched alkylene chain having of from 1 to 15 carbon atoms, which alkylene group may be interrupted by one or more oxygen or sulphur atoms, or by one or more groups of the formula -NR'"-, or =NR'", wherein R'" represents hydrogen or alkyl; or

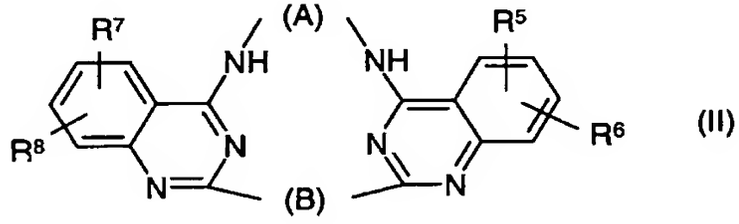
a di-radical of the formula $-(CH_2)_a-D-(CH_2)_b-$, wherein a and b, which may be identical or different, represent the number 0, 1, 2, 3, 4 or 5, and D represents a

cycloalkyl group, or an aryl group of from 6 to 12 carbon atoms, which aryl group may in particular be a phenyl group or a biphenyl group.

In a more preferred embodiment, A and B, independently of each another, represent

decamethylene; octamethylene; hexamethylene; pentamethylene; tetramethylene; trimethylene; dimethylene; N,N'-dimethyl-diamino-methylene; N,N'-dimethyl-diamino-dimethylene; N,N'-dimethyl-diamino-trimethylene; (cis and/or trans)-1,5-cyclooctylene; (cis and/or trans)-1,3-dimethylcyclohexane-α,α'-diyl; para-xylene-α,α'-diyl; meta-xylene-α,α'-diyl; 1,3-phenylene; biphenyl-3,3'-diyl; 4,4'-dimethyl-bibenzyl-α,α'-diyl; 4,4'-dimethyl-diphenylmethane-α,α'-diyl; 4,4'-dimethyl-cis/trans-stilbene-α,α'-diyl; 2,6-bis(4'-methyl-phenyl)pyridine-α,α'-diyl; 3,3'-dimethyl-biphenyl-α,α'-diyl; or 2,7-dimethyl-9H-fluorene-α,α'-diyl.

Formula II



(II)

wherein

A and B, independently of each another, represent

a linear or branched alkylene chain having of from 1 to 15 carbon atoms, which alkylene group may be interrupted by one or more oxygen or sulphur atoms, or by one or more groups of the formula -NR'''-, or =NR''', wherein R''' represents hydrogen or alkyl; or

a di-radical of the formula $-(CH_2)_a-D-(CH_2)_b-$, wherein a and b, which may be identical or different, represent the number 0, 1, 2, 3, 4 or 5, and D represents a cycloalkyl group, or an aryl group of from 6 to 12 carbon atoms, which aryl group may in particular be a phenyl group or a biphenyl group; and

R^5, R^6, R^7 and R^8, independently of each another, represent

halogen, trihalogenmethyl, alkyl, alkenyl, alkynyl, amino, nitro, cyano, or amido, or a group of the formula -R', -OR', -SR', -R'OR", -R'SR", -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', or -C(S)SR'; or

a phenyl or a phenoxy group, which phenyl or phenoxy groups may optionally be substituted on or more times with substituents selected from the group consisting of halogen, trihalogenmethyl, alkyl, alkenyl, alkynyl, amino, nitro, cyano, or amido, or a group of the formula -R', -OR', -SR', -R'OR", -R'SR", -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', or -C(S)SR';

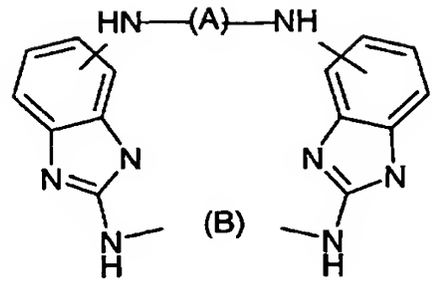
wherein R' and R", independently of each another, represent hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy or alkoxyalkyl, or a group of the formula NR'"R"", wherein R'" and R"", independently of each another, represent hydrogen or alkyl.

In a preferred embodiment, A and B, independently of each another, represent

decamethylene; octamethylene; hexamethylene; pentamethylene; tetramethylene; trimethylene; dimethylene; N,N'-dimethyl-diamino-methylene; N,N'-dimethyl-diamino-dimethylene; N,N'-dimethyl-diamino-trimethylene; (cis and/or trans)-1,5-cyclooctylene; (cis and/or trans)-1,3-dimethylcyclohexane-α,α'-diyl; para-xylene-α,α'-diyl; meta-xylene-α,α'-diyl; 1,3-phenylene; biphenyl-3,3'-diyl; 4,4'-dimethyl-bibenzyl-α,α'-diyl; 4,4'-dimethyl-diphenylmethane-α,α'-diyl; 4,4'-dimethyl-cis/trans-stilbene-α,α'-diyl; 2,6-bis(4'-methyl-phenyl)pyridine-α,α'-diyl; 3,3'-dimethyl-biphenyl-α,α'-diyl; or 2,7-dimethyl-9H-fluorene-α,α'-diyl.

In a most preferred embodiment, the chemical compound of Formula II is 20,23-dimethyl-2,10,18,20,23,25,32,33-octaazahexacyclo [22.7.1.1^{4,8}.1^{11,19}.0^{12,17}.0^{26,31}] tetratriaconta-1(32),11,13,15,17,19(33),24,26,28,30-decaene.

Formula III



(III)

wherein

A and B, independently of each another, represent a linking group having a chain length comprising of from 1 to 20 separate bonds.

In a preferred embodiment, A and B, independently of each another, represent

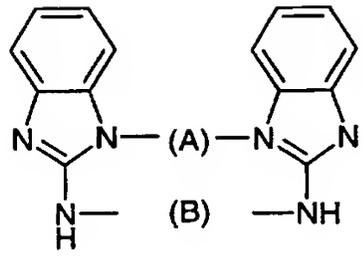
a linear or branched alkylene chain having of from 1 to 15 carbon atoms, which alkylene group may be interrupted by one or more oxygen or sulphur atoms, or by one or more groups of the formula -NR'''-, or =NR''', wherein R''' represents hydrogen or alkyl; or

a di-radical of the formula $-(CH_2)_a-D-(CH_2)_b-$, wherein a and b, which may be identical or different, represent the number 0, 1, 2, 3, 4 or 5, and D represents a cycloalkyl group, or an aryl group of from 6 to 12 carbon atoms, which aryl group may in particular be a phenyl group or a biphenyl group.

In a more preferred embodiment, A and B, independently of each another, represent

decamethylene; octamethylene; hexamethylene; pentamethylene; tetramethylene; trimethylene; dimethylene; N,N'-dimethyl-diamino-methylene; N,N'-dimethyl-diamino-dimethylene; N,N'-dimethyl-diamino-trimethylene; (cis and/or trans)-1,5-cyclooctylene; (cis and/or trans)-1,3-dimethylcyclohexane-α,α'-diyl; para-xylene-α,α'-diyl; meta-xylene-α,α'-diyl; 1,3-phenylene; biphenyl-3,3'-diyl; 4,4'-dimethyl-bibenzyl-α,α'-diyl; 4,4'-dimethyl-diphenylmethane-α,α'-diyl; 4,4'-dimethyl-cis/trans-stilbene-α,α'-diyl; 2,6-bis(4'-methyl-phenyl)pyridine-α,α'-diyl; 3,3'-dimethyl-biphenyl-α,α'-diyl; or 2,7-dimethyl-9H-fluorene-α,α'-diyl.

Formula IV



(IV)

wherein

A and B, independently of each another, represent a linking group having a chain length comprising of from 1 to 20 separate bonds.

In a preferred embodiment, A and B, independently of each another, represent

a linear or branched alkylene chain having of from 1 to 15 carbon atoms, which alkylene group may be interrupted by one or more oxygen or sulphur atoms, or by one or more groups of the formula -NR'''-, or =NR''', wherein R''' represents hydrogen or alkyl; or

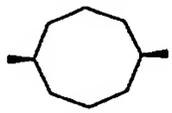
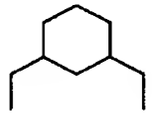
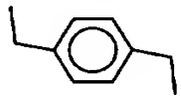
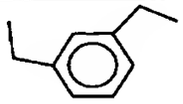
a di-radical of the formula $-(CH_2)_a-D-(CH_2)_b-$, wherein a and b, which may be identical or different, represent the number 0, 1, 2, 3, 4 or 5, and D represents a cycloalkyl group, or an aryl group of from 6 to 12 carbon atoms, which aryl group may in particular be a phenyl group or a biphenyl group.

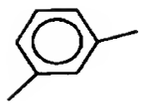
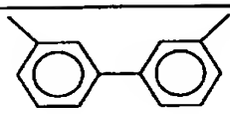
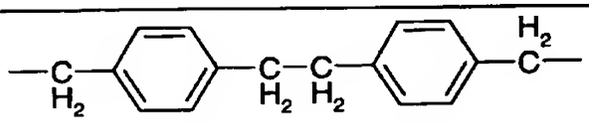
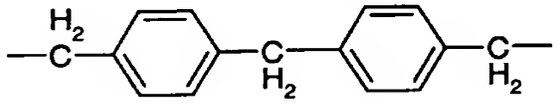
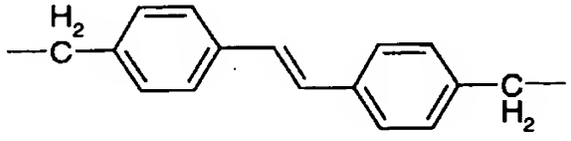
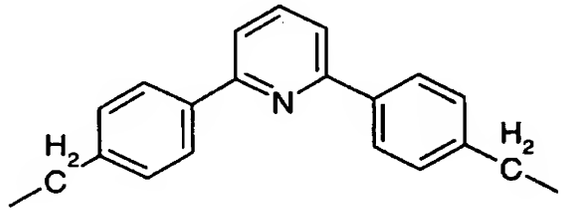
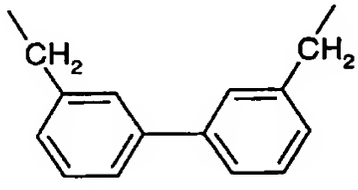
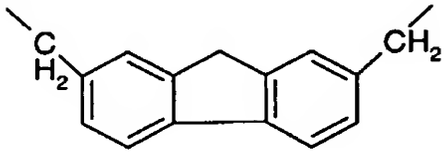
In a more preferred embodiment, A and B, independently of each another, represent

decamethylene; octamethylene; hexamethylene; pentamethylene; tetramethylene; trimethylene; dimethylene; N,N'-dimethyl-diamino-methylene; N,N'-dimethyl-diamino-dimethylene; N,N'-dimethyl-diamino-trimethylene; (cis and/or trans)-1,5-cyclooctylene; (cis and/or trans)-1,3-dimethylcyclohexane-α,α'-diyl; para-xylene-α,α'-diyl; meta-xylene-α,α'-diyl; 1,3-phenylene; biphenyl-3,3'-diyl; 4,4'-dimethyl-bibenzyl-α,α'-diyl; 4,4'-dimethyl-diphenylmethane-α,α'-diyl; 4,4'-dimethyl-cis/trans-stilbene-α,α'-diyl; 2,6-bis(4'-methyl-phenyl)pyridine-α,α'-diyl; 3,3'-dimethyl-biphenyl-α,α'-diyl; or 2,7-dimethyl-9H-fluorene-α,α'-diyl.

Definition of Substituents

In the context of this invention a linking group designates a substituent that links the two parts of the molecule and to bring these parts into a relatively determined spatial inter-relationship. The spacing group may also be termed a spacing group or a bridging group. The linking group of the invention should link the two parts of the molecule in a not too close and not too far distance from each another. It is currently believed that linking groups consisting of from 2 to 20 atoms fulfil this requirement. Examples of such spacing groups are described herein, and summarised below.

Spacing Group	Name
$-(CH_2)_{10}-$	decamethylene;
$-(CH_2)_8-$	octamethylene;
$-(CH_2)_6-$	hexamethylene;
$-(CH_2)_5-$	pentamethylene;
$-(CH_2)_4-$	tetramethylene;
$-(CH_2)_3-$	trimethylene;
$-(CH_2)_2-$	dimethylene;
$-N(CH_3)-CH_2-N(CH_3)-$	N,N'-dimethyl-diamino-methylene;
$-N(CH_3)-CH_2-CH_2-N(CH_3)-$	N,N'-dimethyl-diamino-dimethylene;
$-N(CH_3)-CH_2-CH_2-CH_2-N(CH_3)-$	N,N'-dimethyl-diamino-trimethylene;
	(cis and/or trans)-1,5-cyclooctylene;
	(cis and/or trans)-1,3-dimethylcyclohexane-α,α'-diyl;
	para-xylene-α,α'-diyl;
	meta-xylene-α,α'-diyl;

	1,3-phenylene;
	biphenyl-3,3'-diyl;
	4,4'-dimethyl-bibenzyl-α,α'-diyl;
	4,4'-dimethyl-diphenylmethane-α,α'-diyl;
	4,4'-dimethyl-cis/trans-stilbene-α,α'-diyl;
	2,6-bis(4'-methyl-phenyl)pyridine-α,α'-diyl;
	3,3'-dimethyl-biphenyl-α,α'-diyl;
	2,7-dimethyl-9H-fluorene-α,α'-diyl;

In the context of this invention halogen represents a fluorine, a chlorine, a bromine or a iodine atom.

In the context of this invention an alkyl group designates a univalent saturated, straight or branched hydrocarbon chain. The hydrocarbon chain preferably

contain of from one to eighteen carbon atoms (C_{1-18}-alkyl), more preferred of from one to six carbon atoms (C_{1-6}-alkyl; lower alkyl), including pentyl, isopentyl, neopentyl, tertiary pentyl, hexyl and isohexyl. In a preferred embodiment alkyl represents a C_{1-4}-alkyl group, including butyl, isobutyl, secondary butyl, and tertiary butyl. In a preferred embodiment of this invention alkyl represents a C_{1-3}-alkyl group, which may in particular be methyl, ethyl, propyl or isopropyl.

In the context of this invention a cycloalkyl group designates a cyclic alkyl group, preferably containing of from three to seven carbon atoms (C_{3-7}-cycloalkyl), including cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

In the context of this invention an alkoxy group designates an "alkyl-O-" group, wherein alkyl is as defined above.

In the context of this invention an alkoxy-alkyl group designates an "alkyl-O-alkyl-" group, wherein alkyl is as defined above.

In the context of this invention an amino group may be a primary ($-NH_2$), secondary (-NH-alkyl), or tertiary ($-N(alkyl)_2$) amino group, i.e. it may be substituted once or twice with an alkyl group as defined above.

In the context of this invention a mono- or polycyclic aryl group designates a monocyclic or polycyclic aromatic hydrocarbon group. Examples of preferred aryl groups of the invention are phenyl, naphthyl and anthracenyl.

In the context of this invention an aralkyl group designates a mono- or polycyclic aryl group as defined above, which aryl group is attached to an alkyl group as also defined above. An example of a preferred aralkyl group of the invention benzyl.

In the context of this invention a mono- or poly-heterocyclic group is a mono- or polycyclic compound, which holds one or more heteroatoms in its ring structure. One or more of the ring structures may in particular be aromatic (i.e. a heteroaryl). Preferred heterocyclic monocyclic groups of the invention are 5- or 6 membered heterocyclic monocyclic groups. Examples of preferred heterocyclic monocyclic groups of the invention are furanyl, imidazolyl, isothiazolyl, isoxazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolyl, thiadiazolyl, thiazolyl, and thienyl. Examples of preferred heterocyclic polycyclic groups of the invention are benzimidazolyl, indolyl, isoquinolyl and quinolyl.

Also, in the context of this invention, a chemical compound comprising a tertiary amino group may also be made quaternary (quaternized) using an alkylation agent, in particular an alkyl halide, preferably the chloride, bromide or iodide of methyl or ethyl.

Steric Isomers

The chemical compounds of the present invention may exist in (+) and (-) forms as well as in racemic forms. The racemates of these isomers and the individual isomers themselves are within the scope of the present invention.

Racemic forms can be resolved into the optical antipodes by known methods and techniques. One way of separating the diastereomeric salts is by use of an optically active acid, and liberating the optically active amine compound by treatment with a base. Another method for resolving racemates into the optical antipodes is based upon chromatography on an optical active matrix. Racemic compounds of the present invention can thus be resolved into their optical antipodes, e.g., by fractional crystallisation of d- or l- (tartrates, mandelates, or camphorsulphonate) salts for example.

The chemical compounds of the present invention may also be resolved by the formation of diastereomeric amides by reaction of the chemical compounds of the present invention with an optically active activated carboxylic acid such as that derived from (+) or (-) phenylalanine, (+) or (-) phenylglycine, (+) or (-) camphanic acid or by the formation of diastereomeric carbamates by reaction of the chemical compound of the present invention with an optically active chloroformate or the like.

Additional methods for the resolving the optical isomers are known in the art. Such methods include those described by *Jaques J, Collet A, & Wilen S* in "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York (1981).

Moreover, some of the chemical compounds of the invention being oximes, may thus exist in two forms, syn- and anti-form (Z- and E-form), depending on the arrangement of the substituents around the -C=N- double bond. A chemical compound of the present invention may thus be the syn- or the anti-form (Z- and E-form), or it may be a mixture hereof.

Pharmaceutically Acceptable Salts

The chemical compound of the invention may be provided in any form suitable for the intended administration. Suitable forms include pharmaceutically (i.e. physiologically) acceptable salts, and pre- or prodrug forms of the chemical compound of the invention.

Examples of pharmaceutically acceptable addition salts include, without limitation, the non-toxic inorganic and organic acid addition salts such as the hydrochloride derived from hydrochloric acid, the hydrobromide derived from hydrobromic acid, the nitrate derived from nitric acid, the perchlorate derived from perchloric acid, the phosphate derived from phosphoric acid, the sulphate derived from sulphuric acid, the formate derived from formic acid, the acetate derived from acetic acid, the aconate derived from aconitic acid, the ascorbate derived from ascorbic acid, the benzenesulfonate derived from benzensulfonic acid, the benzoate derived from benzoic acid, the cinnamate derived from cinnamic acid, the citrate derived from citric acid, the embonate derived from embonic acid, the enantate derived from enanthic acid, the fumarate derived from fumaric acid, the glutamate derived from glutamic acid, the glycolate derived from glycolic acid, the lactate derived from lactic acid, the maleate derived from maleic acid, the malonate derived from malonic acid, the mandelate derived from mandelic acid, the methanesulfonate derived from methane sulphonic acid, the naphthalene-2-sulphonate derived from naphtalene-2-sulphonic acid, the phthalate derived from phthalic acid, the salicylate derived from salicylic acid, the sorbate derived from sorbic acid, the stearate derived from stearic acid, the succinate derived from succinic acid, the tartrate derived from tartaric acid, the toluene-p-sulphonate derived from p-toluene sulphonic acid, and the like. Such salts may be formed by procedures well known and described in the art.

Other acids such as oxalic acid, which may not be considered pharmaceutically acceptable, may be useful in the preparation of salts useful as intermediates in obtaining a chemical compound of the invention and its pharmaceutically acceptable acid addition salt.

Metal salts of a chemical compound of the invention includes alkali metal salts, such as the sodium salt of a chemical compound of the invention containing a carboxy group.

The chemical compound of the invention may be provided in dissoluble or indissoluble forms together with a pharmaceutically acceptable solvents such as water, ethanol, and the like. Dissoluble forms may also include hydrated forms such as the monohydrate, the dihydrate, the hemihydrate, the trihydrate, the tetrahydrate, and the like. In general, the dissoluble forms are considered equivalent to indissoluble forms for the purposes of this invention.

Methods of Preparation

The chemical compounds of the invention may be prepared by conventional methods of chemical synthesis, e.g. those described in the working examples. The starting materials for the processes described in the present application are known or may readily be prepared by conventional methods from commercially available chemicals.

The end products of the reactions described herein may be isolated by conventional techniques, e.g. by extraction, crystallisation, distillation, chromatography, etc.

Biological Activity

The chemical compounds of the invention have been subjected to *in vitro* experiments and found particularly useful as potassium channel blocking agents. More particularly the compound of the invention are capable of selectively blockade of SK channels, e.g. SK1, SK2 and/or SK3 channels.

The compounds tested all showed a biological activity determined as IC_{50} in the sub-micromolar and low micromolar range, i.e. of from below 1 to above 10 μM. Preferred compounds of the invention show a biological activity determined as described herein in the in the sub-micromolar and micromolar range, i.e. of from below 1 to about 100 μM.

Therefore, in another aspect, the invention relates to the use of a chemical compound of the invention for the manufacture of medicaments, which medicament may be useful for the treatment or alleviation of a disease or a disorder associated with the activity of potassium channels, in particular SK channels.

In a more preferred embodiment, the chemical compound of the invention may be use for the manufacture of medicaments for the treatment or alleviation of

diseases or conditions like respiratory diseases such as asthma, cystic fibrosis, chronic obstructive pulmonary disease and rhinorrhea, convulsions, vascular spasms, coronary artery spasms, renal disorders, polycystic kidney diseas , bladder spasms, urinary incontinence, bladder outflow obstruction, irritable bowel syndrome, gastrointestinal dysfunction, secretory diarrhoea, ischaemia, cerebral ischaemia, ischaemic hearth disease, angina pectoris, coronary hearth disease, traumatic brain injury, psychosis, anxiety, depression, dementia, memory and attention deficits, Alzheimer's disease, dysmenorrhea, narcolepsy, Reynaud's disease, intermittent claudication, Sjorgren's syndrome, migraine, arrhythmia, hypertension, absence seizures, myotonic muscle dystrophia, xerostomi, diabetes type II, hyperinsulinemia, premature labour, baldness, cancer, and immune suppression.

Pharmaceutical Compositions

In yet another aspect the invention provides novel pharmaceutical compositions comprising a therapeutically effective amount of the chemical compound of the invention.

While a chemical compound of the invention for use in therapy may be administered in the form of the raw chemical compound, it is preferred to introduce the active ingredient, optionally in the form of a physiologically acceptable salt, in a pharmaceutical composition together with one or more adjuvants, excipients, carriers and/or diluents.

In a preferred embodiment, the invention provides pharmaceutical compositions comprising the chemical compound of the invention, or a pharmaceutically acceptable salt or derivative thereof, together with one or more pharmaceutically acceptable carriers therefor and, optionally, other therapeutic and/or prophylactic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Pharmaceutical compositions of the invention may be those suitable for oral, rectal, nasal, topical (including buccal and sub-lingual), transdermal, vaginal or parenteral (including intramuscular, sub-cutaneous and intravenous) administration, or those in a form suitable for administration by inhalation or insufflation.

The chemical compound of the invention, together with a conventional adjuvant, carrier, or diluent, may thus be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, such as tablets or filled capsules, or liquids such as solutions, suspensions, emulsions, elixirs, or capsules filled with the same, all for oral use, in the form of suppositories for rectal administration; or in the form of sterile injectable solutions for parenteral (including subcutaneous) use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed.

The chemical compound of the present invention can be administered in a wide variety of oral and parenteral dosage forms. It will be obvious to those skilled in the art that the following dosage forms may comprise, as the active component, either a chemical compound of the invention or a pharmaceutically acceptable salt of a chemical compound of the invention.

For preparing pharmaceutical compositions from a chemical compound of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavouring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from five or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active

compound with encapsulating material as carrier providing a capsule in which the activ component, with or without carriers, is surrounded by a carri r, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glyceride or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized moulds, allowed to cool, and thereby to solidify.

Compositions suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Liquid preparations include solutions, suspensions, and emulsions, for example, water or water-propylene glycol solutions. For example, parenteral injection liquid preparations can be formulated as solutions in aqueous polyethylene glycol solution.

The chemical compound according to the present invention may thus be formulated for parenteral administration (e.g. by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulation agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilization from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavours, stabilising and thickening agents, as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, or other well known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavours, stabilisers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like

For topical administration to the epidermis the chemical compound according to the invention may be formulated as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents.

Compositions suitable for topical administration in the mouth include lozenges comprising the active agent in a flavoured base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerine or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The compositions may be provided in single or multi-dose form. In the latter case of a dropper or pipette, this may be achieved by the patient administering an appropriate, predetermined volume of the solution or suspension. In the case of a spray, this may be achieved for example by means of a metering atomising spray pump.

Administration to the respiratory tract may also be achieved by means of an aerosol formulation in which the active ingredient is provided in a pressurised pack with a suitable propellant such as a chlorofluorocarbon (CFC) for example dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane, carbon dioxide, or other suitable gas. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by provision of a metered valve.

Alternatively the active ingredients may be provided in the form of a dry powder, for example a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and

polyvinylpyrrolidone (PVP). Conveniently the powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form for example in capsules or cartridges of, e.g., gelatin, or blister packs from which the powder may be administered by means of an inhaler.

In compositions intended for administration to the respiratory tract, including intranasal compositions, the compound will generally have a small particle size for example of the order of 5 microns or less. Such a particle size may be obtained by means known in the art, for example by micronization.

When desired, compositions adapted to give sustained release of the active ingredient may be employed.

The pharmaceutical preparations are preferably in unit dosage forms. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packaged tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

Tablets or capsules for oral administration and liquids for intravenous administration and continuous infusion are preferred compositions.

Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing Co., Easton, PA).

A therapeutically effective dose refers to that amount of active ingredient which ameliorates the symptoms or condition. Therapeutic efficacy and toxicity, e.g. ED_{50} and LD_{50}, may be determined by standard pharmacological procedures in cell cultures or experimental animals. The dose ratio between therapeutic and toxic effects is the therapeutic index and may be expressed by the ratio LD_{50}/ED_{50}. Pharmaceutical compositions which exhibit large therapeutic indexes are preferred.

The dose administered must of course be carefully adjusted to the age, weight and condition of the individual being treated, as well as the route of administration, dosage form and regimen, and the result desired, and the exact dosage should of course be determined by the practitioner.

The active ingredient may be administered in one or several doses per day. It is presently contemplated that compositions containing of from about 0.1 to about 500 mg of active ingredient per unit dosage, preferably of from about 1 to about 100 mg, most preferred of from about 1 to about 10 mg, are suitable for therapeutic treatments.

Methods of Treatment

In another aspect the invention relates to a method of treating or alleviating a disorder or disease of a living animal body, including a human, which disorder or disease is responsive to blockade of the potassium channel, in particular the SK channel, which method comprises comprising administering to such a living animal body, including a human, in need thereof a therapeutically-effective amount of a compound of the invention.

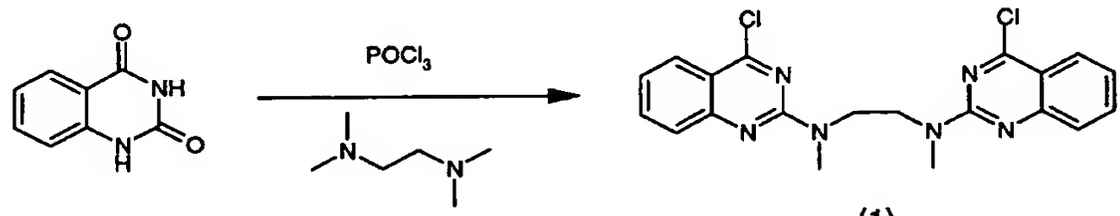
The In a preferred embodiment of the method of the invention, the disease or disorder is asthma, cystic fibrosis, chronic obstructive pulmonary disease and rhinorrhea, convulsions, vascular spasms, coronary artery spasms, renal disorders, polycystic kidney disease, bladder spasms, urinary incontinence, bladder outflow obstruction, irritable bowel syndrome, gastrointestinal dysfunction, secretory diarrhoea, ischaemia, cerebral ischaemia, ischaemic hearth disease, angina pectoris, coronary hearth disease, traumatic brain injury, psychosis, anxiety, depression, dementia, memory and attention deficits, Alzheimer's disease, dysmenorrhea, narcolepsy, Reynaud's disease, intermittent claudication, Sjorgren's syndrome, migraine, arrhythmia, hypertension, absence seizures, myotonic muscle dystrophia, xerostomi, diabetes type II, hyperinsulinemia, premature labour, baldness, cancer, and immune suppression.

A satisfactory result can, in certain instances, be obtained at a dosage as low as 0.005 mg/kg i.v. and 0.01 mg/kg p.o. The upper limit of the dosage range is about 10 mg/kg i.v. and 100 mg/kg p.o. Preferred ranges are from about 0.001 to about 1 mg/kg i.v. and from about 0.1 to about 10 mg/kg p.o.

EXAMPLES

The invention is further illustrated with reference to the following examples which are not intended to be in any way limiting to the scope of the invention as claimed.

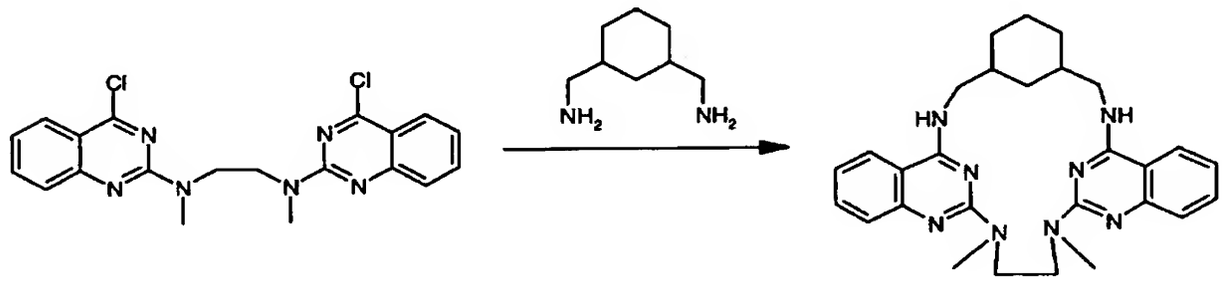
Example 1



(1)

N,N'-bis(4-chloroquinoxalin-2-yl)-N,N'-dimethylethylenediamine (Compound 1)

A suspension of benzoyleneurea (5.0 g; 30.8 mmol) in phosphoroxychloride (70 ml) was stirred under N_2 and N,N,N,N-tetramethylethylendiamine (16.33 ml; 108 mmol) was added. The mixture was heated to reflux overnight. The cooled mixture was filtered and the precipitate was washed with dichloromethane. The combined filtrate and washings was concentrated under reduced pressure. Aqueous sodium hydroxide (1 M) was carefully added to the concentrate and the resulting suspension was extracted with dichloromethane. This extract was dried over magnesium sulphate, concentrated under reduced pressure and eluted through silica gel with a mixture of ethyl acetate and ligroin (1:4 v/v) to yield Compound 1 (0.65 g, 5%).



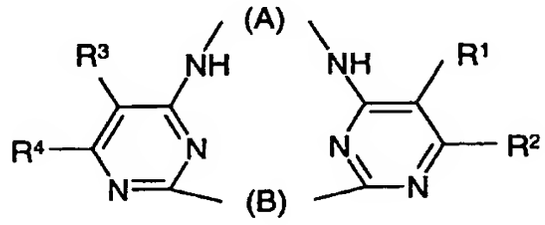
(1) (2)

20,23-dimethyl-2,10,18,20,23,25,32,33-octaazahexacyclo [22.7.1.1^{4,8}.1^{11,19}.0^{12,17}.0^{26,31}] tetratriaconta-1(32),11,13,15,17,19(33),24,26,28,30-decaene (Compound 2)

To a solution of 1,3-cyclohexanebis(methylamine) (0.2 ml; 1.35 mmol) in anhydrous DMF (70 ml) was added N,N'-bis(4-chloroquinoxalin-2-yl)-N,N'-dimethylethylenediamine (Compound 1; 0.56 g; 1.35 mmol) and the mixture was stirred at 100°C for ten days. The solvent was distilled off at reduced pressure and the residue was triturated with water to leave the crystalline crude product, which was purified by column-chromatography on silica gel using a mixture of dichloromethane, methanol and aqueous ammonia (90:10:1 v/v/v) as the eluent. Yield of Compound 2: 0.1g (15%). M.p. 284-285°C.

CLAIMS

1. A chemical compound represented by the general formula I,



(I)

wherein

A and B, independently of each another, represent a linking group having a chain length comprising of from 1 to 20 separate bonds; and

R^1, R^2, R^3 and R^4, independently of each another, represent

hydrogen, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, amino, trihalogenmethyl, nitro, cyano, or a group of the formula -OR', -SR', -R'OR", -R'SR", -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', -C(S)SR', -C(O)NR'(OR"), -C(S)NR'(OR"), -C(O)NR'(SR"), -C(S)NR'(SR"), $-CH(CN)_2$, $-C(O)NR'_2$, $-C(S)NR'_2$, $-CH[C(O)R']_2$, $-CH[C(S)R']_2$, $-CH[C(O)OR']_2$, $-CH[C(S)OR']_2$, $-CH[C(O)SR']_2$, $-CH[C(S)SR']_2$, CH_2OR', CH_2SR', or $-SO_2NR'R"$;

a partially or completely saturated mono- or polycyclic group, a mono- or poly-heterocyclic group, an aralkyl group, or a hetero-alkyl group, which mono- or polycyclic groups or aralkyl or hetero-alkyl groups may optionally be substituted one or more times with substituents selected from the group consisting of

halogen, trihalogenmethyl, alkyl, alkenyl, alkynyl, amino, nitro, cyano, or amido, or a group of the formula -R', -OR', -SR', -R'OR", -R'SR", -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', or -C(S)SR'; or

a phenyl or a phenoxy group, which phenyl or phenoxy groups may optionally be substituted on or more times with substituents selected from the

group consisting of halogen, trihalogenmethyl, alkyl, alkenyl, alkynyl, amino, nitro, cyano, or amido, or a group of the formula -R', -OR', -SR', -R'OR", -R'SR", -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', or -C(S)SR'; or

R^1 and R^2 together, or R^3 and R^4 together, form a partially or completely saturated mono- or polycyclic group, or a mono- or poly-heterocyclic group, which mono- or polycyclic groups may optionally be substituted one or more times with substituents selected from the group consisting of

halogen, trihalogenmethyl, alkyl, alkenyl, alkynyl, amino, nitro, cyano, or amido, or a group of the formula -R', -OR', -SR', -R'OR", -R'SR", -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', or -C(S)SR'; or

a phenyl or a phenoxy group, which phenyl or phenoxy groups may optionally be substituted on or more times with substituents selected from the group consisting of halogen, trihalogenmethyl, alkyl, alkenyl, alkynyl, amino, nitro, cyano, or amido, or a group of the formula -R', -OR', -SR', -R'OR", -R'SR", -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', or -C(S)SR';

wherein R' and R", independently of each another, represent hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy or alkoxyalkyl, or a group of the formula NR'"R"", wherein R'" and R"", independently of each another, represent hydrogen or an alkyl group.

2. The chemical compound according to claim 1, wherein A and B, independently of each another, represent

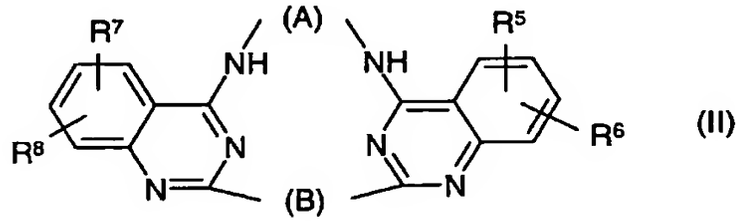
a linear or branched alkylene chain having of from 1 to 15 carbon atoms, which alkylene group may be interrupted by one or more oxygen or sulphur atoms, or by one or more groups of the formula -NR'"-, or =NR'", wherein R'" represents hydrogen or alkyl; or

a di-radical of the formula $-(CH_2)_a-D-(CH_2)_b-$, wherein a and b, which may be identical or different, represent the number 0, 1, 2, 3, 4 or 5, and D represents a cycloalkyl group, or an aryl group of from 6 to 12 carbon atoms, which aryl group may in particular be a phenyl group or a biphenyl group.

3. The chemical compound according to claim 2, wherein A and B, independently of each another, represent

decamethylene; octamethylene; hexamethylene; pentamethylene; tetramethylene; trimethylene; dimethylene; N,N'-dimethyl-diamino-methylene; N,N'-dimethyl-diamino-dimethylene; N,N'-dimethyl-diamino-trimethylene; (cis and/or trans)-1,5-cyclooctylene; (cis and/or trans)-1,3-dimethylcyclohexane-α,α'-diyl; para-xylene-α,α'-diyl; meta-xylene-α,α'-diyl; 1,3-phenylene; biphenyl-3,3'-diyl; 4,4'-dimethyl-bibenzyl-α,α'-diyl; 4,4'-dimethyl-diphenylmethane-α,α'-diyl; 4,4'-dimethyl-cis/trans-stilbene-α,α'-diyl; 2,6-bis(4'-methyl-phenyl)pyridine-α,α'-diyl; 3,3'-dimethyl-biphenyl-α,α'-diyl; or 2,7-dimethyl-9H-fluorene-α,α'-diyl.

4. A chemical compound represented by the general formula II,



(II)

wherein A and B, independently of each another, represent

a linear or branched alkylene chain having of from 1 to 15 carbon atoms, which alkylene group may be interrupted by one or more oxygen or sulphur atoms, or by one or more groups of the formula -NR'''-, or =NR''', wherein R''' represents hydrogen or alkyl; or

a di-radical of the formula $-(CH_2)_a-D-(CH_2)_b-$, wherein a and b, which may be identical or different, represent the number 0, 1, 2, 3, 4 or 5, and D represents a cycloalkyl group, or an aryl group of from 6 to 12 carbon atoms, which aryl group may in particular be a phenyl group or a biphenyl group; and

R^5, R^6, R^7 and R^8, independently of each another, represent

halogen, trihalogenmethyl, alkyl, alkenyl, alkynyl, amino, nitro, cyano, or amido, or a group of the formula -R', -OR', -SR', -R'OR", -R'SR", -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', or -C(S)SR'; or

a phenyl or a phenoxy group, which phenyl or phenoxy groups may optionally be substituted on or more times with substituents selected from the group consisting of halogen, trihalogenmethyl, alkyl, alkenyl, alkynyl, amino, nitro, cyano, or amido, or a group of the formula -R', -OR', -SR', -R'OR", -R'SR", -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', or -C(S)SR';

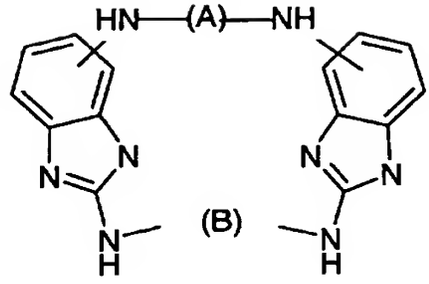
wherein R' and R", independently of each another, represent hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy or alkoxyalkyl, or a group of the formula NR'"R"", wherein R'" and R"", independently of each another, represent hydrogen or alkyl.

5. The chemical compound of claim 4, wherein A and B, independently of each another, represent

decamethylene; octamethylene; hexamethylene; pentamethylene; tetramethylene; trimethylene; dimethylene; N,N'-dimethyl-diamino-methylene; N,N'-dimethyl-diamino-dimethylene; N,N'-dimethyl-diamino-trimethylene; (cis and/or trans)-1,5-cyclooctylene; (cis and/or trans)-1,3-dimethylcyclohexane-α,α'-diyl; para-xylene-α,α'-diyl; meta-xylene-α,α'-diyl; 1,3-phenylene; biphenyl-3,3'-diyl; 4,4'-dimethyl-bibenzyl-α,α'-diyl; 4,4'-dimethyl-diphenylmethane-α,α'-diyl; 4,4'-dimethyl-cis/trans-stilbene-α,α'-diyl; 2,6-bis(4'-methyl-phenyl)pyridine-α,α'-diyl; 3,3'-dimethyl-biphenyl-α,α'-diyl; or 2,7-dimethyl-9H-fluorene-α,α'-diyl.

6. The chemical compound of claim 4, being 20,23-dimethyl-2,10,18,20,23,25,32,33-octaazahexacyclo [22.7.1.1^{4,8}.1^{11,19}.0^{12,17}.0^{26,31}] tetratriaconta-1(32),11,13,15,17,19(33),24,26,28,30-decaene.

7. A chemical compound represented by the general formula III,



(III)

wherein

A and B, independently of each another, represent a linking group having a chain length comprising of from 1 to 20 separate bonds.

8. The chemical compound according to claim 7, wherein A and B, independently of each another, represent

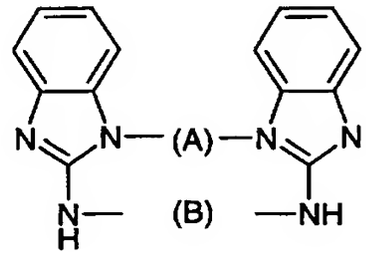
a linear or branched alkylene chain having of from 1 to 15 carbon atoms, which alkylene group may be interrupted by one or more oxygen or sulphur atoms, or by one or more groups of the formula -NR'''-, or =NR''', wherein R''' represents hydrogen or alkyl; or

a di-radical of the formula $-(CH_2)_a-D-(CH_2)_b-$, wherein a and b, which may be identical or different, represent the number 0, 1, 2, 3, 4 or 5, and D represents a cycloalkyl group, or an aryl group of from 6 to 12 carbon atoms, which aryl group may in particular be a phenyl group or a biphenyl group

9. The chemical compound according to claim 7, wherein A and B, independently of each another, represent

decamethylene; octamethylene; hexamethylene; pentamethylene; tetramethylene; trimethylene; dimethylene; N,N'-dimethyl-diamino-methylene; N,N'-dimethyl-diamino-dimethylene; N,N'-dimethyl-diamino-trimethylene; (cis and/or trans)-1,5-cyclooctylene; (cis and/or trans)-1,3-dimethylcyclohexane-α,α'-diyl; para-xylene-α,α'-diyl; meta-xylene-α,α'-diyl; 1,3-phenylene; biphenyl-3,3'-diyl; 4,4'-dimethyl-bibenzyl-α,α'-diyl; 4,4'-dimethyl-diphenylmethane-α,α'-diyl; 4,4'-dimethyl-cis/trans-stilbene-α,α'-diyl; 2,6-bis(4'-methyl-phenyl)pyridine-α,α'-diyl; 3,3'-dimethyl-biphenyl-α,α'-diyl; or 2,7-dimethyl-9H-fluorene-α,α'-diyl.

10. A chemical compound represented by the general formula IV,



(IV)

wherein

A and B, independently of each another, represent a linking group having a chain length comprising of from 1 to 20 separate bonds.

11. The chemical compound according to claim 10, wherein A and B, independently of each another, represent

a linear or branched alkylene chain having of from 1 to 15 carbon atoms, which alkylene group may be interrupted by one or more oxygen or sulphur atoms, or by one or more groups of the formula -NR'''-, or =NR''', wherein R''' represents hydrogen or alkyl; or

a di-radical of the formula $-(CH_2)_a-D-(CH_2)_b-$, wherein a and b, which may be identical or different, represent the number 0, 1, 2, 3, 4 or 5, and D represents a cycloalkyl group, or an aryl group of from 6 to 12 carbon atoms, which aryl group may in particular be a phenyl group or a biphenyl group

12. The chemical compound according to claim 10, wherein A and B, independently of each another, represent

decamethylene; octamethylene; hexamethylene; pentamethylene; tetramethylene; trimethylene; dimethylene; N,N'-dimethyl-diamino-methylene; N,N'-dimethyl-diamino-dimethylene; N,N'-dimethyl-diamino-trimethylene; (cis and/or trans)-1,5-cyclooctylene; (cis and/or trans)-1,3-dimethylcyclohexane-α,α'-diyl; para-xylene-α,α'-diyl; meta-xylene-α,α'-diyl; 1,3-phenylene; biphenyl-3,3'-

diyl; 4,4'-dimethyl-bibenzyl-α,α'-diyl; 4,4'-dimethyl-diphenylmethane-α,α'-diyl; 4,4'-dimethyl-cis/trans-stilbene-α,α'-diyl; 2,6-bis(4'-methyl-phenyl)pyridine-α,α'-diyl; 3,3'-dimethyl-biphenyl-α,α'-diyl; or 2,7-dimethyl-9H-fluorene-α,α'-diyl.

13. The chemical compound according to any of claims 1-12, for use as a medicament.

14. A pharmaceutical composition comprising an effective amount of a chemical compound according to claims 1-12.

15. Use of the chemical compound of claims 1-12 for the manufacture of a medicament for the treatment or alleviation of diseases or disorders associated with the activity of potassium channels.

16. The use according to claim 15, wherein the disease or disorder is asthma, cystic fibrosis, chronic obstructive pulmonary disease and rhinorrhea, convulsions, vascular spasms, coronary artery spasms, renal disorders, polycystic kidney disease, bladder spasms, urinary incontinence, bladder outflow obstruction, irritable bowel syndrome, gastrointestinal dysfunction, secretory diarrhoea, ischaemia, cerebral Ischaemia, ischaemic hearth disease, angina pectoris, coronary hearth disease, traumatic brain injury, psychosis, anxiety, depression, dementia, memory and attention deficits, Alzheimer's disease, dysmenorrhea, narcolepsy, Reynaud's disease, intermittent claudication, Sjorgren's syndrome, migraine, arrhythmia, hypertension, absence selzures, myotonic muscle dystrophia, xerostomi, diabetes type II, hyperinsulinemia, premature labour, baldness, cancer, and immune suppression.

17. A method of treating or alleviating a disorder or disease of a living animal body, including a human, which disorder or disease is responsive to blockade of the potassium channel, which method comprises comprising administering to such a living animal body, including a human, in need thereof a therapeutically-effective amount of a compound of any of claims 1 to 12.

18. The method according to claim 17, wherein the disease or disorder is asthma, cystic fibrosis, chronic obstructive pulmonary disease and rhinorrhea, convulsions, vascular spasms, coronary artery spasms, renal disorders, polycystic kidney disease, bladder spasms, urinary incontinence, bladder outflow obstruction, irritable bowel syndrome, gastrointestinal dysfunction, secretory diarrhoea, ischaemia, cerebral ischaemia, ischaemic hearth disease, angina pectoris, coronary hearth disease, traumatic brain injury, psychosis, anxiety, depression, dementia, memory and attention deficits, Alzheimer's disease, dysmenorrhea, narcolepsy, Reynaud's disease, intermittent claudication, Sjorgren's syndrome, migraine, arrhythmia, hypertension, absence seizures, myotonic muscle dystrophia, xerostomi, diabetes type II, hyperinsulinemia, premature labour, baldness, cancer, and immune suppression.

TITLE: POTASSIUM CHANNEL BLOCKING AGENTS

ABSTRACT

This invention relates to novel potassium channel blocking agents, and their use in the preparation of pharmaceutical compositions.

Moreover the invention is directed to pharmaceutical compositions useful for the treatment or alleviation of diseases or disorders associated with the activity of potassium channels, in particular asthma, cystic fibrosis, chronic obstructive pulmonary disease and rhinorrhea, convulsions, vascular spasms, coronary artery spasms, renal disorders, polycystic kidney disease, bladder spasms, urinary incontinence, bladder outflow obstruction, irritable bowel syndrome, gastrointestinal dysfunction, secretory diarrhoea, ischaemia, cerebral ischaemia, ischaemic hearth disease, angina pectoris, coronary hearth disease, traumatic brain injury, psychosis, anxiety, depression, dementia, memory and attention deficits, Alzheimer's disease, dysmenorrhea, narcolepsy, Reynaud's disease, intermittent claudication, Sjorgren's syndrome, migraine, arrhythmia, hypertension, absence seizures, myotonic muscle dystrophia, xerostomi, diabetes type II, hyperinsulinemia, premature labour, baldness, cancer, and immune suppression.